Remarks

In reply to the Office Action mailed August 22, 2007, Applicants amended claims 86, 117 and 119. It is believed that no new matter is entered by way of the amendment and its entry is respectfully requested. Claims 86, 89, 90, 94-98, 100-102, and 110-119 are pending and under examination.

It is believed that the above amendments and the following remarks address and overcome each of the outstanding rejections to the claims. Reconsideration of each of the rejections is therefore respectfully requested.

Priority

On page 2 of the Office Action, the Examiner has stated that Applicants cannot rely on the foreign priority document to overcome any prior art rejections because translation of the foreign priority document has not been made of record. Submitted herewith is a certified translation of foreign priority document DE 103 02 421, claiming a priority date of January 21, 2003.

Rejections under 35 USC 112, second paragraph

On page 3 of the Office Action, the Examiner has rejected claims 117 and 119 as being indefinite because they recite the limitation "the target gene." Applicants have amended claims 117 and 119 to obviate this rejection. The claims as amended are directed to "the target RNA." As such, Applicants respectfully request that rejections relating to there being insufficient antecedent basis for the limitation "the target gene" may be withdrawn.

Rejections under 35 USC 103

The Examiner has rejected claims 86, 89, 94-98, 100-102 and 110-119 as being unpatentable over Rana in view of Florence, "Manoharan I", and Cook and evidenced by "Manoharan II". Applicants traverse and respectfully request reconsideration based on the following remarks.

The claimed invention recites a double-stranded ribonucleic acid (dsRNA) including a complementary RNA strand, a sense RNA strand and only one lipophilic

group having a $\log K_{ow}$ exceeding 1. The complementary RNA strand has a nucleotide sequence which is complementary to a target RNA. The target RNA is an mRNA transcript of a target gene or of a (+) strand RNA virus. The lipophilic group is either covalently attached to a 5'-end of the complementary RNA strand wherein a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group, or the lipophilic group is covalently attached to a 5'-end of the sense RNA strand. Applicants submit that the references, both alone and when read in combination, would not render obvious the claimed invention.

Rana discloses compositions for RNA interference and related methods and further discloses modifications of the RNA. On page 4 of the Office Action, Examiner concedes that Rana does not teach that lipophilic group has a $\log K_{ow}$ exceeding 1, that the lipophilic group is a sterol or carbamate linked cholesteryl, or that the said lipophilic group is linked at 5' end with a phosphodiester group. Without such a teaching, Rana also fails to teach the required positioning of such a lipophilic group on an RNA strand as recited in the claims. The Examiner relies upon paragraph [0033] of Rana for generally teaching modification of the 3' end, 5', end or both ends of an RNA. However, Applicants do not generally claim any of any modification of an RNA strand, but rather have specifically recited a required number, only one, of a specific modification, that of the recited lipophilic group, at a specific location on the RNA strand. Applicants submit that these claim requirements are simply not taught in Rana and that the remaining cited references to not cure the deficiencies of Rana.

On page 5 of the Office Action, the Examiner states that Florence teaches that "lipophilic dendrimers, PAMAM, are efficient drug delivery vehicle for molecules because the dendrimer is small and can translocate across the cell layer." However, Fluorence does not disclose or suggest attachment of a lipophilic group to an RNA strand as recited in the claims, i.e., the use of "only one" lipophilic group attached at a specific portion of an RNA strand. In fact, the only examples provided by Florence shows that a PAMAM dendrimer without any associated drug/molecule is absorbed in certain tissues. As shown in figure 1 of Florence, the PAMAM dendrimer provides no easily discernible covalent linking point for linking a drug molecule to the dendrimer. As there is no readily available covalent linking point on the dendrimer and Florence provides no

guidance as to how to possibly covalently link the dendrimer with the drug, there would have been no motivation to use this dendrimer in view of Florence's statement of unpredictability of the effect of incorporation of drug molecules on the uptake process.

Moreover, Florence does not teach $\log K_{ow}$ as an essential characteristic of delivery with the PAMAM dendrimer. Florence suggests no connection between $\log K_{ow}$ exceeding 1 and the delivery potential of the PAMAM dendrimer. Florence only mentions $\log K_{ow}$ value for the PAMAM dendrimer in passing and makes no suggestions as to if $\log K_{ow}$ exceeding 1 is the essential element of delivery by PAMAM dendrimer. On the other hand, Florence repeatedly states that there is an optimum size for nanoparticluate uptake, and all the examples in Florence reflect this (pages 253, 254 and 256-258). Florence's repeated references to an optimal size of dendrimer for delivery would not have led one skilled in the art to use dendrimers with $\log K_{ow}$ exceeding one. Accordingly, the combination of Florence with Rana does not render obvious Applicants claimed invention.

Both Monoharan I and Cook are cited for the teaching of increasing the stability of a nucleic acid by the conjugation of a lipophilic group, for example, cholesterol. However, neither "Manoharan I" nor Cook discloses, teaches or suggests that only a single conjugated ligand has a $\log K_{ow}$ exceeding one conjugated to an RNA as specifically recited in the instant invention. However, both Monoharan I and Cook disclose a large number of derivatized oligonucleotides, including derivatives falling outside of the recited claims, which require "only one" of a specific ligand, at a specified position on the RNA. Nothing either Monoharan I or Cook would suggest the modifications required to arrive at the claimed compound. For example, although the Examiner has cited Monoharan I and Cook for the disclosures of the conjugation of a lipophilic group, in paragraphs 0032 and 0035, Manoharan also describes use of water soluble vitamin conjugates. It is known in the Art that water soluble molecules usually have $\log K_{ow}$ values less than 1. "Manoharan I" does not provide critical teaching or suggestions that would lead the skilled artisan to adopt ligands with $\log K_{ow}$ exceeding one as opposed to ligands with $\log K_{ow}$ less than one. Similarly, Cook describes a number of ligands but does not provide the critical teaching or suggestion that would lead the skilled artisan to adopt ligands with $\log K_{ow}$ exceeding one as opposed to ligands with

$\log K_{ow}$ less than one. Accordingly, neither Manoharan I nor Cook cure the deficiencies of Florence and Rana.

Finally, Applicants assert that the Examiner is incorrect in concluding that "Manoharan II" teaches that "one can synthesize an ideal drug with predictable results." Moreover, certainly nothing in "Manoharan II" would lead one of skill in the art to make the specifically claimed compound, nor is Monoharan II relied upon for such a teaching. Instead, Monoharan II simply provides a general review of conjugates as "potential antisense drugs."

Because the teachings of Rana, Floerence, "Manoharan I", Cook and "Manoharan II", either alone or in combination would not lead one in the art to arrive at the claimed invention the cited references do not support a *prima facie* case of obviousness. Thus, withdrawal of the rejections is respectfully requested.

Summary

Applicants have amended the claims and provided arguments to address the outstanding rejection of the claims. It is believed that the rejections have been addressed and that the application is in condition for allowance.

Please apply any charges or credits to Deposit Account No 37462, referencing Attorney Docket Number A2038-7052US.

Respectfully submitted,
Hadwiger et al., Applicant

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